REMARKS/ARGUMENTS

With entry of this amendment, claims 36 and 39-49 are pending in this application. Independent claims 36 and 46 are amended to substantially incorporate the limitation of claim 38 by specifying an analog of an "acceptor" substrate of core 2 GlcNAc transferase. Accordingly, to avoid any inconsistency or redundancy in the claims, claims 37 and 38 are canceled. No new matter is added by these amendments. Applicants reserve the right to pursue any canceled subject matter, including claims of original scope, in a related, co-pending application. In view of these amendments and the remarks set forth herein, Applicants respectfully request reconsideration of the application.

Examiner Interview

Applicants thank the Examiner for the teleconference of January 24, 2007, with the undersigned, during which issues pertaining to the cited art and enablement were discussed. Applicants' representative understands from the Interview that claim amendments, substantially incorporating the acceptor substrate analog limitation of claim 38 into the independent claims, would be sufficient to overcome the present art rejections under 35 U.S.C. § 102. With respect to the enablement issue, while no specific agreement was reached, Applicants' representative understands that the Examiner would consider additional arguments supporting enablement of methods directed to a genus of compounds as presently recited in the claims. This response serves to enter theses amendments and additional arguments.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 36 and 38-49 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. The Examiner, having accepted Applicants' evidentiary submissions showing "the ability of substrate analogs of various glycosyltransferases (e.g. defined, small molecules) to reach the desired target and inhibit [a] target transferase," (Office Action at p. 3), now contends that the claims are not enabled for acceptor substrate

analogs as encompassed by the claims. According to the Examiner, "the ability of these small substrate analogs to provide for physiological effects is neither correlative nor representative of the ability of substrate acceptor analogs of core 2 GlcNAc transferase to reach the target cell subcellular organelles in the required quantity to provide inhibition and treatment effects in an organism." (*Id.*) This rejection is traversed as set forth below.

First, as Applicants' representative understands from the Examiner Interview of January 24, 2007, this rejection stems from the Examiner's concern that the genus of compounds encompassed by acceptor substrate analogs of core 2 GlcNAc transferase includes larger molecules (*e.g.*, long, branching polymers) that might be inaccessible to cells, and thereby unable to effect a physiological response *in vivo*. If Applicants' representative has misinterpreted the Examiner's concern in any way, clarification is respectfully requested.

While Applicants acknowledge that a genus of acceptor substrate analog inhibitors for a glycosyltransferase can encompass larger, polymeric molecules, Applicants note that (1) the genus encompasses small molecules that can compete with or specifically inhibit glycosylation of an acceptor substrate of core 2 GlcNAc transferase and (2) a person skilled in the pertinent art would be able to readily determine whether any particular acceptor substrate analog is so large as to be inaccessible to cells in the bloodstream. Applicants will address these points in detail below.

With regard to the nature of molecules encompassed by the recited genus of acceptor substrate analog inhibitors, as noted during the Examiner Interview of January 24, 2007, both donor and acceptor substrates of glycosyltransferases are similar in that these substrates are essentially sugars. Accordingly, inhibitors that are analogs of an acceptor substrate would tend to have many biophysical and/or structural features in common with inhibitors that are analogs of a donor substrate. Furthermore, acceptor substrates of a glycosyltransferase can be small oligosaccharide structures, and thus a class of acceptor substrate analog inhibitors includes, *e.g.*, small molecule inhibitors that compete with the acceptor.

With respect to cell accessibility, the Examiner has essentially accepted Applicants' previous arguments regarding accessibility of substrate analog inhibitors into cells

present in the bloodstream so as to exert a corresponding physiological effect, at least insofar as donor substrate analog inhibitors are concerned. Because, as discussed above, the recited genus of acceptor substrate analog inhibitors would share many biophysical and/or structural features in common with donor substrate analogs and also includes small molecules that specifically inhibit glycosylation of the acceptor, Applicants believe that these arguments are applicable to the present claims.

To briefly reiterate these arguments, the desired mammalian target cells in the instant case are leukocytes, which are present in the bloodstream. Because the target cells are present in the bloodstream, effective inhibitor concentrations can be readily achieved, for example, by known methods for systemic administration of pharmaceutical agents, including, *e.g.*, i.v. administration or absorption through the gut. As discussed in Applicants' previous response, targeting to cells in the bloodstream is already believed predictable in view of Camenish *et al.*, which demonstrates the ability to determine passive diffusion of small molecules based on readily available biophysical parameters. Once present in the bloodstream, inhibitors having the ability to passively cross cellular membranes (as predicted, for example, by the method of Camenisch *et al.*) would be expected to passively diffuse into target leukocytes and into the appropriate subcellular organelle to exert a physiological effect.

Furthermore, inhibitors of glycosyltransferases were, as a class of inhibitors, already shown in the art as being capable of targeting the appropriate subcellular organelle of cells in the bloodstream to exert a corresponding physiological effect *in vivo*, as previously evidenced by Exhibits D and E (respectively, Morin *et al.* (*J. Cell. Physiol.* 114:162-172, 1983) and Kijima-Suda *et al.* (*Cancer Research* 46:858-862, 1986)). The inhibitors used in these particular studies were small molecules, each having structures based at least in part on a glycosyltransferase substrate (*e.g.*, tunicamycin, an analog of UDP-GlcNAc (*see* Morin), and KI-8110, a sialic acid:nucleoside conjugate having sialyltransferase inhibiting activity that specifically depends on the acceptor (*see* Kijima-Suda)). In each case, the inhibitor was found to enter cells to exert physiological effects, including relevant *in vivo* effects as shown in Kijima-Suda. Because acceptor substrate analog inhibitors would also have structures based at least in

part on sugar substrates, the skilled artisan would readily and reasonably accept that Morin and Kijima-Suda are also representative of the ability of small molecule acceptor substrate analog inhibitors to enter cells and exert corresponding effects either *in vivo* on cells in the bloodstream.

As to the Examiner's concern that a genus of acceptor substrate analog inhibitors encompasses molecules that are too large or otherwise inaccessible to cells in the bloodstream, Applicants first note that such embodiments are not encompassed by the present claims. The claims require inhibition of an inflammatory response in the mammal (*see* claim 36) or inhibition of binding of a first myeloid cell to an endothelial cell or to a second myeloid cell (*see* claim 46). Implicit in the recitation of these physiological effects is the requirement that the inhibitor be accessible to the target cells in the bloodstream. For reasons already substantially set forth in previous responses as filed on June 5, 2006, and November 23, 2005, a person skilled in the pertinent art would be able to readily determine whether any particular acceptor substrate analog is accessible to cells in the bloodstream, such as by evaluation of biophysical parameters as evidenced by Camenisch *et al.*, or simply by routine testing on cells *in vitro*.

For at least the reasons above, and in addition to reasons previously of record, the present claims are enabled by the specification as filed. Accordingly, withdrawal of the present rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

The claims currently stand rejected under 35 U.S.C. § 102(b) as follows:

claims 36, 39-43, and 46-49 as allegedly anticipated by Morin *et al.* (*Cancer Res.* 43:4, 1983);

claims 36, 39-43, and 46-49 as allegedly anticipated by Kyung Book Univ (Kyung Book Univ., Enterprising form/report No. 911-0403-007-2, 1991); and

claim 36, 37, 39-43, and 46-49 as allegedly anticipated by DeClercq *et al.* (*Biochem. J.* 205:1-13, 1982).

While Applicants do not agree with the present rejections, these rejections are overcome by the present amendments substantially incorporating the limitation of claim 38 into independent claims 36 and 46, from which all other claims depend, as well as the cancellation of claim 37. Applicants note that claim 38 is not subject to any of these rejections. Accordingly, and consistent with discussions during the Examiner Interview of January 24, 2007, the presently amended claims are novel over the cited art. Withdrawal of these rejections is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: February 26, 2007

Nicholas V. Sherbina
Reg. No. 54,443

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-030
NVS:jae
60988607 v1